

**METHOD FOR TREATING A MUCUS SECRETION**

**CROSS-REFERENCE**

5        This application is a continuation-in-part of  
serial number 09/487,477, filed January 19, 2000, which  
is a divisional of serial number 08/627,118, filed  
April 3, 1996, which is a continuation of serial number  
08/173,996, filed December 28, 1993, now abandoned.

10       **FIELD OF THE INVENTION**

15       The present invention provides novel methods for  
treating various disorders and conditions, with a  
botulinum toxin, including excessive mucus secretions.  
Importantly, the present invention provides methods  
useful in relieving pain related to muscle activity or  
contracture and therefore is of advantage in the  
treatment of, for example, muscle spasm such as  
20       Temporomandibular Joint Disease, low back pain,  
myofascial pain, pain related to spasticity and  
dystonia, as well as sports injuries, and pain related  
to contractures in arthritis.

25       **BACKGROUND OF THE INVENTION**

30       Heretofore, Botulinum toxins, in particular  
Botulinum toxin type A, has been used in the treatment  
of a number of neuromuscular disorders and conditions  
involving muscular spasm; for example, strabismus,  
blepharospasm, spasmodic torticollis (cervical  
dystonia), oromandibular dystonia and spasmodic  
dysphonia (laryngeal dystonia). The toxin binds  
rapidly and strongly to presynaptic cholinergic nerve  
35       terminals and inhibits the exocytosis of acetylcholine

**BOOKS**

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30           The term Botulinum toxin is a generic term embracing the family of toxins produced by the anaerobic bacterium *Clostridium botulinum* and, to date, seven immunologically distinct neurotoxins have been identified. These have been given the designations A, 35 B, C, D, E, F and G. For further information con-

cerning the properties of the various Botulinum toxins, reference is made to the article by Jankovic and Brin, *The New England Journal of Medicine*, No. 17, 1990, pp. 1186-1194, and to the review by Charles L. Hatheway in Chapter 1 of the book entitled *Botulinum Neurotoxin and Tetanus Toxin*, L. L. Simpson, Ed., published by Academic Press Inc. of San Diego, California, 1989, the disclosures in which are incorporated herein by reference.

The neurotoxic component of Botulinum toxin has a molecular weight of about 150 kilodaltons and is thought to comprise a short polypeptide chain of about 50 kD which is considered to be responsible for the toxic properties of the toxin, i.e., by interfering with the exocytosis of acetylcholine, by decreasing the frequency of acetylcholine release, and a larger polypeptide chain of about 100 kD which is believed to be necessary to enable the toxin to bind to the presynaptic membrane.

The "short" and "long" chains are linked together by means of a simple disulfide bridge. (It is noted that certain serotypes of Botulinum toxin, e.g., type E, may exist in the form of a single chain un-nicked protein, as opposed to a dichain. The single chain form is less active but may be converted to the corresponding dichain by nicking with a protease, e.g., trypsin. Both the single and the dichain are useful in the method of the present invention.)

In general, four physiologic groups of *C. botulinum* are recognized (I, II, III, IV). The organisms capable of producing a serologically distinct toxin may come from more than one physiological group. For ex-

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The present invention comprises a method for treating a mucus secretion of a patient by local administration to a patient an effective amount of a botulinum toxin (A, B, C, D, E, F or G) in order to reduce a mucus secretion of the patient. The mucus secretion is not a symptom of rhinorrhea. The mucus secretion can be a cholinergic influenced mucus secretion. The botulinum toxin can be administered in an amount of between 0.01 units and 5000 units, such as between 0.01 unit and 500 units.

A detailed embodiment of the present invention comprises a method for treating a cholinergic influenced mucus secretion of a human patient by administering to a human patient a therapeutically effective amount of botulinum toxin type A in order to reduce the mucus secretion, wherein the mucus secretion is not a symptom of rhinorrhea. A further method for treating a mucus secreting gland can comprise the step of administering to a mucus secreting gland a botulinum toxin thereby reducing a mucus secretory activity of the gland, wherein the mucus secretion is not a symptom of rhinorrhea. The gland can be an excessively secreting mucus gland influenced by the cholinergic nervous system. The botulinum toxin can be administered by injection into the mucus gland or into the local area of the mucus gland.

Another detailed embodiment of the present invention can comprise a method for treating an excessively secreting mucus gland, the method comprising the step of injecting an excessively secreting, cholinergic nervous system influenced mucus gland or local mucus gland area of a human patient with

a therapeutically effective amount of botulinum toxin type A in order to reduce the excessive mucus gland secretion, wherein the mucus secretion is not a symptom of rhinorrhea.

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# **DETAILED DESCRIPTION**

The Botulinum toxins used according to the present invention are Botulinum toxins type A, B, C, D, E, F and G.

The physiologic groups of *Clostridium botulinum* types are listed in Table I.

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**Table I. Physiologic Groups of *Clostridium botulinum***

Group	Toxin Sero-Type	Biochemistry	Milk Digest	Glucose Fermentation	Lipase	Phages & Plasmids	Phenotypically Related <i>Clostridium</i> (nontoxigenic)
I	A,B,F	proteolytic saccharolytic	+	+	+	+	<i>C. sporogenes</i>
II	B,E,F	nonproteolytic saccharolytic psychotrophic	-	+	+	+	
III	C,D	nonproteolytic saccharolytic	+	+	+	+	<i>C. novyi</i>
IV	G	proteolytic nonsaccharolytic	+	-	-	-	<i>C. subterminale</i>

These toxin types may be produced by selection from the appropriate physiologic group of *Clostridium botulinum* organisms. The organisms designated as Group I are usually referred to as proteolytic and produce Botulinum toxins of types A, B and F. The organisms designated as Group II are saccharolytic and produce Botulinum toxins of types B, E and F. The organisms designated as Group III produce only Botulinum toxin types C and D and are distinguished from organisms of Groups I and II by the production of significant amounts of propionic acid. Group IV organisms only

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produce neurotoxin of type G. The production of any and all of the Botulinum toxin types A, B, C, D, E, F and G are described in Chapter 1 of *Botulinum Neurotoxin and Tetanus Toxin*, cited above, and/or the references cited therein. Botulinum toxins types B, C, D, E, F and G are also available from various species of clostridia.

Currently fourteen species of clostridia are considered pathogenic. Most of the pathogenic strains produce toxins which are responsible for the various pathological signs and symptoms. Organisms which produce Botulinum toxins have been isolated from botulism outbreaks in humans (types A, B, E and F) and animals (types C and D). Their identities were described through the use of specific antitoxins (antibodies) developed against the earlier toxins. Type G toxin was found in soil and has low toxigenicity. However, it has been isolated from autopsy specimens, but thus far there has not been adequate evidence that type G botulism has occurred in humans.

Preferably, the toxin is administered by means of intramuscular injection directly into a local area such as a spastic muscle, preferably in the region of the neuromuscular junction, although alternative types of administration (e.g., subcutaneous injection), which can deliver the toxin directly to the affected region, may be employed where appropriate. The toxin can be presented as a sterile pyrogen-free aqueous solution or dispersion and as a sterile powder for reconstitution into a sterile solution or dispersion.

Where desired, tonicity adjusting agents such as sodium chloride, glycerol and various sugars can be



added. Stabilizers such as human serum albumin may also be included. The formulation may be preserved by means of a suitable pharmaceutically acceptable preservative such as a paraben, although preferably it is  
5 unpreserved.

It is preferred that the toxin is formulated in unit dosage form; for example, it can be provided as a sterile solution in a vial or as a vial or sachet  
10 containing a lyophilized powder for reconstituting a suitable vehicle such as saline for injection.

In one embodiment, the Botulinum toxin is formulated in a solution containing saline and pasteurized human serum albumin, which stabilizes the  
15 toxin and minimizes loss through non-specific adsorption. The solution is sterile filtered (0.2 micron filter), filled into individual vials and then vacuum-dried to give a sterile lyophilized powder. In use,  
20 the powder can be reconstituted by the addition of sterile unpreserved normal saline (sodium chloride 0.9% for injection).

The dose of toxin administered to the patient will  
25 depend upon the severity of the condition; e.g., the number of muscle groups requiring treatment, the age and size of the patient and the potency of the toxin.

The potency of the toxin is expressed as a multiple of the  $LD_{50}$  value for the mouse, one unit (U) of toxin  
30 being defined as being equivalent to that amount of toxin that kills 50% of a group of 18 to 20 female Swiss-Webster mice, weighing between 17-22 grams each.

The dosages used in human therapeutic applications  
35 are roughly proportional to the mass of muscle being

injected. Typically, the dose administered to the patient may be up from about 0.01 to about 1,000 units; for example, up to about 500 units, and preferably in the range from about 80 to about 460 units per patient  
5 per treatment, although smaller or larger doses may be administered in appropriate circumstances such as up to about 50 units for the relief of pain and in controlling cholinergic secretions.

10 As the physicians become more familiar with the use of this product, the dose may be changed. In the Botulinum toxin type A, available from Porton, DYSPORT, 1 nanogram (ng) contains 40 units. 1 ng of the Botulinum toxin type A, available from Allergan, Inc.,  
15 i.e., BOTOX®, contains 4 units. The potency of Botulinum toxin and its long duration of action mean that doses will tend to be administered on an infrequent basis. Ultimately, however, both the quantity of toxin administered and the frequency of its  
20 administration will be at the discretion of the physician responsible for the treatment and will be commensurate with questions of safety and the effects produced by the toxin.

25 In some circumstances, particularly in the relief of pain associated with sports injuries, such as, for example, charleyhorse, botulinum type F, having a short duration activity, is preferred.

30 Mucus coats many epithelial surfaces and is secreted into fluids such as saliva. Mucus is composed chiefly of mucins and inorganic salts suspended in water. Mucus adheres to many epithelial surfaces where it serves as a diffusion barrier against contact with  
35 noxious substances (such as gastric acid and smoke) and

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A treatment of an excessive mucus secretion according to the present invention excludes treatment of rhinorrhea because of *inter alia*: (a) the possibility that local administration of a botulinum toxin to the highly vascularized nasal mucosal cells can result in entry of botulinum toxin into the systemic circulation; (b) the considerable sensitivity of inflamed nasal mucosal glands to local administration of a pharmaceutical, and; (c) the typically brief duration of the condition of rhinorrhea (days), as compared to the longevity of the effect of administration of a botulinum toxin (months).

The invention will now be illustrated by reference to the following nonlimiting examples.

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In each of the examples, appropriate areas of each  
5 patient are injected with a sterile solution containing  
the confirmation of Botulinum toxin. Total patient  
doses range from about 0.01 units to about 10,000 units  
(i.e. of type B toxin) of a botulinum toxin. Before  
injecting any muscle group, careful consideration is  
10 given to the anatomy of the muscle group, the aim being  
to inject the area with the highest concentration of  
neuromuscular junctions, if known. Before injecting  
the muscle, the position of the needle in the muscle is  
confirmed by putting the muscle through its range of  
15 motion and observing the resultant motion of the needle  
end. General anaesthesia, local anaesthesia and  
sedation are used according to the age of the patient,  
the number of sites to be injected, and the particular  
needs of the patient. More than one injection and/or  
20 sites of injection may be necessary to achieve the  
desired result. Also, some injections, depending on  
the muscle to be injected, may require the use of fine,  
hollow, teflon-coated needles, guided by  
electromyography.

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Following injection, it is noted that there are no  
systemic or local side effects and none of the patients  
are found to develop extensive local hypotonicity. The  
majority of patients show an improvement in function  
30 both subjectively and when measured objectively.

Example 1

The Use of Botulinum toxin Type in the Treatment  
of Tardive Dyskinesia

5       A male patient, age 45, suffering from tardive  
dyskinesia resulting from the treatment with an  
antipsychotic drug, such as Thorazine or Haldol, is  
treated with 150 units of Botulinum toxin type B by  
direct injection of such toxin into the facial muscles.  
10    After 1-3 days, the symptoms of tardive dyskinesia,  
i.e., orofacial dyskinesia, athetosis, dystonia,  
chorea, tics and facial grimacing, etc. are markedly  
reduced.

Example 1(a)

15       The method of Example 1 is repeated, except that  
a patient suffering from tardive dyskinesia is injected  
with 50-200 units of Botulinum toxin type C. A similar  
20    result is obtained.

Example 1(b)

25       The method of Example 1 is repeated, except that  
a patient suffering from tardive dyskinesia is injected  
with 50-200 units of Botulinum toxin type D. A similar  
result is obtained.

Example 1(c)

30       The method of Example 1 is repeated, except that  
a patient suffering from tardive dyskinesia is injected  
with 50-200 units of Botulinum toxin type E. A similar  
result is obtained.

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Example 1(d)

The method of Example 1 is repeated, except that a patient suffering from tardive dyskinesia is injected with 50-200 units of Botulinum toxin type F. A similar result is obtained.

Example 1(e)

The method of Example 1 is repeated, except that a patient suffering from tardive dyskinesia is injected with 50-200 units of Botulinum toxin type G. A similar result is obtained.

Example 2

The Use of Botulinum toxin Type B in the Treatment of Spasmodic Torticollis

A male, age 45, suffering from spasmodic torticollis, as manifested by spasmodic or tonic contractions of the neck musculature, producing stereotyped abnormal deviations of the head, the chin being rotated to one side, and the shoulder being elevated toward the side at which the head is rotated, is treated by injection with 100-1,000 units of Botulinum toxin type E. After 3-7 days, the symptoms are substantially alleviated; i.e., the patient is able to hold his head and shoulder in a normal position.

Example 2(a)

The method of Example 2 is repeated, except that a patient suffering from spasmodic torticollis is injected with 100-1,000 units of Botulinum toxin type B. A similar result is obtained.

Example 2(b)

5 The method of Example 2 is repeated, except that  
a patient suffering from spasmodic torticollis is  
injected with 100-1,000 units of Botulinum toxin type  
C. A similar result is obtained.

Example 2(c)

10 The method of Example 2 is repeated, except that  
a patient suffering from spasmodic torticollis is  
injected with 100-1,000 units of Botulinum toxin type  
D. A similar result is obtained.

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Example 2(d)

20 The method of Example 2 is repeated, except that  
a patient suffering from spasmodic torticollis is  
injected with 100-1,000 units of Botulinum toxin type  
E. A similar result is obtained.

Example 2(e)

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The method of Example 2 is repeated, except that  
a patient suffering from spasmodic torticollis is  
injected with 100-1,000 units of Botulinum toxin type  
F. A similar result is obtained.

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**Example 2(f)**

5 The method of Example 2 is repeated, except that  
a patient suffering from spasmodic torticollis is  
injected with 100-1,000 units of Botulinum toxin type  
G. A similar result is obtained.

**Example 3**

10 **The Use of Botulinum toxin in the Treatment of**  
**Essential Tremor**

15 A male, age 45, suffering from essential tremor,  
which is manifested as a rhythmical oscillation of head  
or hand muscles and is provoked by maintenance of  
posture or movement, is treated by injection with 50-  
1,000 units of Botulinum toxin type B. After two to  
eight weeks, the symptoms are substantially alleviated;  
i.e., the patient's head or hand ceases to oscillate.

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**Example 3(a)**

25 The method of Example 3 is repeated, except that  
a patient suffering from essential tremor is injected  
with 100-1,000 units of Botulinum toxin type C. A  
similar result is obtained.

**Example 3(b)**

30 The method of Example 3 is repeated, except that  
a patient suffering from essential tremor is injected  
with 100-1,000 units of Botulinum toxin type D. A  
similar result is obtained.



Example 3(c)

5 The method of Example 3 is repeated, except that  
a patient suffering from essential tremor is injected  
with 100-1,000 units of Botulinum toxin type E. A  
similar result is obtained.

Example 3(d)

10 The method of Example 3 is repeated, except that  
a patient suffering from essential tremor is injected  
with 100-1,000 units of Botulinum toxin type F. A  
similar result is obtained.

15 Example 3(e)

The method of Example 3 is repeated, except that  
a patient suffering from essential tremor is injected  
with 100-1,000 units of Botulinum toxin type G. A  
20 similar result is obtained.

Example 4

The Use of Botulinum toxin in the Treatment of  
Spasmodic Dysphonia

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A male, age 45, unable to speak clearly, due to  
spasm of the vocal chords, is treated by injection of  
the vocal chords with Botulinum toxin type B, having an  
activity of 80-500 units. After 3-7 days, the patient  
30 is able to speak clearly.

The method of Example 4 is repeated, except that a patient suffering from spasmodic dysphonia is injected with 80-500 units of Botulinum toxin type C. A similar result is obtained.

10       The method of Example 4 is repeated, except that  
a patient suffering from spasmodic dysphonia is  
injected with 80-500 units of Botulinum toxin type D.  
A similar result is obtained.

The method of Example 4 is repeated, except that a patient suffering from spasmodic dysphonia is injected with 80-500 units of Botulinum toxin type E. 20 A similar result is obtained.

The method of Example 4 is repeated, except that  
25 a patient suffering from spasmodic dysphonia is  
injected with 80-500 units of Botulinum toxin type F.  
A similar result is obtained.

The method of Example 4 is repeated, except that a patient suffering from spasmodic dysphonia is injected with 8-500 units of Botulinum toxin type G. A similar result is obtained.

Example 5

The Use of Botulinum toxin Types A-G in the Treatment  
of Excessive Sweating, Lacrimation or Mucus Secretion  
or Other Cholinergic Controlled Secretions

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A male, age 65, with excessive unilateral sweating is treated by administering 0.01 to 50 units, of Botulinum toxin, depending upon degree of desired effect. The larger the dose, usually the greater spread and duration of effect. Small doses are used initially. Any serotype toxin alone or in combination could be used in this indication. The administration is to the gland nerve plexus, ganglion, spinal cord or central nervous system to be determined by the physician's knowledge of the anatomy and physiology of the target glands and secretory cells. In addition, the appropriate spinal cord level or brain area can be injected with the toxin (although this would cause many effects, including general weakness). Thus, the gland (if accessible) or the nerve plexus or ganglion are the targets of choice. Excessive sweating, tearing (lacrimation), mucus secretion or gastrointestinal secretions are positively influenced by the cholinergic nervous system. Sweating and tearing are under greater cholinergic control than mucus or gastric secretion and would respond better to toxin treatment. However, mucus and gastric secretions could be modulated through the cholinergic system. All symptoms would be reduced or eliminated with toxin therapy in about 1-7 days. Duration would be weeks to several months.

An excessive intestinal mucus secretion can be treated by injecting about 40 units of a botulinum toxin type A or about 2000 units of a botulinum toxin type B into the hyperactive intestinal mucosa.

Example 6

The Use of Botulinum toxin Types A-G in the Treatment  
of Muscle Spasms in Smooth Muscle Disorders Such As  
Sphincters of the Cardiovascular Arteriole,  
Gastrointestinal System, Urinary or Gall Bladder,  
Rectal, Etc.

10 A male, age 30-40, with a constricted pyloric  
valve which prevents his stomach from emptying, is  
treated by administering 1-50 units of Botulinum toxin.  
The administration is to the pyloric valve (which  
controls release of stomach contents into the  
15 intestine) divided into 2 to 4 quadrants, injections  
made with any endoscopic device or during surgery. In  
about 1-7 days, normal emptying of the stomach,  
elimination or drastic reduction in regurgitation  
occurs.

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Example 7

The Use of Botulinum toxin Types A-G in the Treatment  
of Muscle Spasms and Control of Pain Associated with  
Muscle Spasms in Temporal Mandibular Joint Disorders

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A female, age 35, is treated by administration of  
0.1 to 50 units total of Botulinum toxin. The  
administration is to the muscles controlling the  
closure of the jaw. Overactive muscles may be  
30 identified with EMG (electromyography) guidance.  
Relief of pain associated with muscle spasms, possible  
reduction in jaw clenching occurs in about 1-3 days.

Example 8

The Use of Botulinum toxin Types A-G in the Treatment  
of Muscle Spasms and Control of Pain Associated with  
Muscle Spasms in Conditions Secondary to Sports  
5 Injuries (Charleyhorse)

10 A male, age 20, with severe cramping in thigh  
after sports injury is treated by administration of a  
short duration toxin, possible low dose (0.1-25 units)  
of preferably type F to the muscle and neighboring  
muscles which are in contraction ("cramped"). Relief  
of pain occurs in 1-7 days.

Example 9

15 The Use of Botulinum toxin Types A-G in the Treatment  
of Muscle Spasms and Control of Pain Associated with  
Muscle Spasms in Smooth Muscle Disorders Such as  
Gastrointestinal Muscles

20 A female, age 35, with spastic colitis, is treated  
with 1-100 units of Botulinum toxin divided into  
several areas, enema (1-5 units) delivered in the  
standard enema volume, titrate dose, starting with the  
lowest dose. Injection is to the rectum or lower colon  
25 or a low dose enema may be employed. Cramps and pain  
associated with spastic colon are relieved in 1-10  
days.

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Example 10

The Use of Botulinum toxin Types A-G in the Treatment  
of Muscle Spasms and Control of Pain Associated with  
Muscle Spasms in Spasticity Conditions Secondary to  
Stroke, Traumatic Brain or Spinal Cord Injury

A male, age 70, post-stroke or cerebral vascular event, is injected with 50 to 300 units of Botulinum toxin in the major muscles involved in severe closing of hand and curling of wrist and forearm or the muscles involved in the closing of the legs such that the patient and attendant have difficulty with hygiene. Relief of these symptoms occurs in 7 to 21 days.

Example 11

The Use of Botulinum toxin Types A-G in the Treatment  
of Patients with Swallowing disorders

A patient with a swallowing disorder caused by excessive throat muscle spasms is injected with about 1 to about 300 units of Botulinum toxin in the throat muscles. Relief the swallowing disorder occurs in about 7 to about 21 days.

Example 12

The Use of Botulinum toxin Types A-G in the Treatment  
of Patients with Tension Headache

A patient with a tension headache caused by excessive throat muscle spasms is injected with about 1 to about 300 units of Botulinum toxin in muscles of the head and upper neck. Relief of the tension headache occurs in about 1 to about 7 days.

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